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Association between tumor markers (CA125, CA15-3) and homozygous sickle cell anemia

CA125 and CA15-3 in homozygous sickle cell anemia

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Abstract

Aim: Sickle Cell Anemia (SCA) is a systemic and chronic inflammatory disease and is one of the most common hemoglobinopathies in the world and in our country. Cancer antigen 15-3 (CA15-3) and cancer antigen (CA125) have an important place in cancer screening, treatment follow-up and disease follow-up today. However, it has been shown that it may be high in some diseases other than these purposes. In this study, we also planned to determine the relationship between tumor markers and patients with SCA, which is a chronic inflammatory and ischemic disease.

Material and Methods: Patients over the age of 18 who were diagnosed with homozygous SCA and followed up in the Department of Internal Diseases of Hatay Mustafa Kemal University Health Practice and Research Hospital and applied to the outpatient clinic were included in the study. Height, weight, body mass index (BMI) and waist circumference of all patients were measured. Echocardiographic examination was performed. Blood samples were collected from the patients to study CA125 and CA15-3 on appropriate days and conditions.

Results: A total of 34 patients, 19 female and 15 male, and 35 healthy volunteers, 16 female and 19 male, were included in the study. In the echocardiographic examinations, the ejection fraction was normal in the control and SCA groups, and no signs of pericardial effusion were found. The mean CA15-3 of the patients with SCA was 56.42±23.73 U/ml, the mean of CA15-3 of the control group was 9.99±4.62 U/ml, and there was a statistically significant difference (p=0,001). The median CA125 value of patients with SCA was calculated as 5.95 U/ml, while the highest was 99 U/ml and the lowest was 1.8 U/ml. While the median CA125 value of the control group was calculated as 6 U/ml, the highest measurement was 17.8 U/ml and the lowest measurement was 0.7 U/ml. There was no any statistically significant difference between the groups.

Discussion: Although the CA15-3 level was high in patients with SCA, the CA125 level was normal. We think that CA15-3 level is important in understanding the pathophysiology and mechanism of SCA and in terms of follow-up. Our study should be supported by studies with large patient participation.

Keywords
Sickle Cell Anemia, CA125, CA15-3

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Introduction

Sickle Cell Anemia (SCA) is a systemic, inflammatory, chronic disease with acute attacks and chronic organ damage, and is one of the most common monogenic hemoglobinopathies in the world and in our country [1]. Hb S, which occurs abnormally due to the mutation in the β-globin chain, causes clinical findings of the disease. SCA is inherited with autosomal recessive inheritance [2] .

Sickle Cell Disease (SCD) is the common term for all genotypes with clinical manifestations and is a common disease in countries such as Africa, South America, the Caribbean and Central America, Saudi Arabia, Italy, India, Greece and Turkey, affecting millions of people around the World [3]. It is common in our country, especially in the Mediterranean region.

Hb S causes erythrocytes to sickle and these erythrocytes lose their ability to change shape over time, thus causing tissue infarcts and ischemia while crossing the capillaries. As a result, various clinical pictures and complications are seen, from acute painful crisis to priapism. Sickled erythrocytes cause recurrent painful crises, damage to organs and loss of function [2] .

Today, tumor markers have an important place in cancer screening, treatment follow-up and disease follow-up. However, apart from these purposes, it has been shown that tumor markers may be high in some diseases. CA125 can be found to be high in conditions such as pelvic inflammatory disease, acute hepatitis, cirrhosis, systemic lupus erythematosus, pericarditis, congestive heart failure and peritoneal infections [4], while CA15-3 can be found to be high in cirrhosis, tuberculosis, sarcoidosis, pelvic inflammatory disease, pregnancy and lactation[5].

In this study, we planned to investigate the relationship between the disease and CA125 and CA15-3 in patients with SCA, which is a chronic inflammatory and ischemic disease.

Material and Methods

Patients

Approval from Mustafa Kemal University Clinical Research Ethics Committee was obtained prior to the study (Approval no: 19/01/2017/13). Thirty-four patients over the age of 18 and 35 healthy individuals diagnosed with homozygous SCA, followed by the Department of Internal Diseases of Hatay Mustafa Kemal University Health Practice and Research Hospital, were included in the study. Patients with homozygous SCA included in the study were included in the study during the asymptomatic period when acute complications such as stroke, acute chest syndrome, priapism, and painful crisis were not experienced for at least three months. The criteria for exclusion from the study were as follows: age under 18, being in the acute complication period, blood transfusion history in the last 3 months, presence of concomitant disease, diabetes mellitus, hypertension, heart failure, pregnancy and lactation, drug addiction, abnormality in kidney and liver function tests, presence of neurological and psychiatric disease. Healthy individuals who were similar in terms of age, weight, height and BMI to the patients with SCA were included in the control group. Ejection fraction and pericardial effusion findings were investigated in echocardiographic examinations in the control and SCA groups. Venous blood was collected from the patients on suitable days, after 12 hours of fasting, between 08:00 and 10:30 in the morning, into gel tubes with vacuum EDTA and without anticoagulant. It was centrifuged at 4000 rpm for 10 minutes, hemolysate was prepared and the serum and plasma portions were stored in 1.5 ml Eppendorf tubes at -70 degrees. Samples CA15-3 and CA 125 were studied with Siemens Advia Centaur hormone device by the immunosense method.

Statistical analysis

SPSS22.0 program was used in the analysis of the variables. The conformity of univariate data to normal distribution was evaluated with the Shapiro-Wilk test, and the variance coefficients and homogeneity of variance were evaluated with the Levene's test. In the comparison of two independent groups, the Independent-Samples T-test was used together with the Bootstrap results, while the Mann-Whitney U test was used with the Monte Carlo simulation technique. Fisher's Exact test was used to compare categorical variables with each other. Quantitative variables were shown in the tables as mean ± std. (standard deviation) and median range (maximum-minimum), while categorical variables were shown as n (%).Variables were analyzed at the 95% confidence level, and those with a p-value less than 0.05 were considered significant.

Results

A total of 34 patients, 19 female and 15 male, and 35 healthy volunteers, 16 female and 19 male, were included in the study. Demographic and statistical data of the control and patient groups are presented in Table 1.

While the mean age of the patients with SCA was 29.44±7.89 years, the mean age of the control group was 29.97±7.57. While the mean height of the patients with SCA was 1.67±0.08 m, the mean height of the control group was 1.70±0.09 m. While the mean weight of the patients with SCA was 59.71±10.11 kg, the mean weight of the control group was 62.71±8.86 kg. While the

Table 1. Comparison of control and patient groups.

	Control (n=35)	Patient (n=34)	Total (N=69)	P value
	n (%)			
Gender				
Male	19 (54,3)	15 (44,1)	34 (49,3)	0,473
Female	16 (45,7)	19 (55,9)	35 (50,7)	
	Mean±SD.			
Age (year)	29,97±7,57	29,44±7,89	29,71±7,68	0,772
Height (meter)	1,70±0,09	1,67±0,08	1,69±0,08	0,11
Weight (kg)	62,71±8,86	59,71±10,11	61,23±9,54	0,198
BMI	21,56±2,06	21,05±3,15	21,31±2,65	0,445
CA15-3	9,99±4,62	56,42±23,73	32,87±28,82	0,001
	Median (Max.-Min.)			
CA125	6 (17,8-0,7)	5,95 (99-1,8)	6 (99-0,7)	0,144
Waist circumference (cm)	83 (102-61)	85 (110-50)	85 (110-50)	0,171

Table 2. Comparison of CA15-3 and CA125 values in control and patient groups

	Control group	Patient group	P value
CA 15-3 (Mean±SD)	9,99±4,62	56,42±23,73	0,001
CA 125 Median (Max.-Min.)	6 (17,8-0,7)	5,95 (99-1,8)	0,144

median waist circumference of the patients with SCA was 85 cm, the maximum value was 110 cm, and the minimum value was 50 cm, the median value of the waist circumference of the control group was 83 cm, the maximum value was 102 cm, and the minimum value was 61 cm. The mean body mass index of the patients with SCA was 21.05±3.15, and the mean BMI of the control group was 21.56±2.06. In the echocardiographic examinations, the ejection fraction was normal in the control and SCA groups, and there was no evidence of pericardial effusion.

CA15-3 and CA125 values in the Control and Patient Group are shown in Table 2. The mean CA15-3 of the patients with SCA was 56.42±23.73U/ml, the mean of CA15-3 of the control group was 9.99±4.62U/ml, and there was a statistically significant difference (p=0.001).

The median CA125 value of patients with SCA was calculated as 5.95U/ml, while the highest was 99U/ml and the lowest was 1.8U/ml. While the median CA125 value of the control group was calculated as 6U/ml, the highest measurement was 17.8U/ml and the lowest measurement was 0.7U/ml. There was no statistically significant difference between the groups (p>0,05). CA15-3 distribution in the patient group was between 46.7-56.3 U/ml in 9 patients, between 35-45.6 U/ml in 6 patients, between 57.9-68U/ml in 5 patients, and 68.4-77.8U in 5 patients. It was measured between 25.7-34.3 U/ml in 3 patients, between 16.5-21.8 U/ml in 2 patients, and between 91.4-98.8 U/ml in 2 patients.

Discussion

Sickle cell anemia is important because it is a hematological disease with high morbidity and mortality and its frequency is high in our region. As it is known, tumor markers are not only used in cancer diagnosis and treatment follow-up today. It has been previously shown that these markers can be elevated for many benign reasons. In our study, we investigated whether there is a relationship between CA125 and CA15-3 and SCA, which is a chronic inflammatory and ischemic disease. For this purpose, we compared the values of CA15-3 and CA125 between venous blood collected from patients and healthy individuals, which we collected with appropriate criteria. We found the mean of CA15-3 56.42±23.73U/ml in SCA patients and 9.99±4.62 U/ml in the control group, and we found statistically significant differences. In our literature research, we found that there are some studies supporting our results.

The occurrence of malignancy in patients with SCA has been demonstrated in individual cases or small series studies. In their study, Shultz et al. emphasized that there is no clear information about how often or which type of cancer is seen more frequently in patients with SCA, and that the risk of developing cancer may increase with the use of hydroxyurea [6]. In the data published by The International Association of Sickle Cell Nurses and Physician Assistants (IASCNAPA), an international organization dealing with patients with SCA, it was reported that 52 cancer cases (49 patients) were detected in 16,613 patients [6]. In a single-center study by Dawkins et al., 696 patients with SCA were followed for 10 years. The age range of these patients was 18-79 years. Cancer was detected in 5 patients during the follow-up period and the cancer incidence rate was reported as 5/2864 or 1.74/1000. During the follow-up, 68 of the patients died and the cause of death in 3 of them was found to be cancer [7].

Shokunbi et al., reported that they detected hemangioendothelioma of the hip bone in their 35-year-old patient with SCD [8]. Baron et al. examined 117 African-American patients with renal cell cancer diagnosed at the University of Chicago between 1952-1992. They stated that 3 of these patients were SCA and 11 were sickle cell carriers. They found that the median age of renal cell cancer in patients with SCA was 36, while the median age was 55 in sickle cell carriers. They reported that the development of renal cell carcinoma may be due to kidney damage caused by sickling and the possible immunosuppressive effect of multiple blood transfusions and these could be considered as risk factors. They suggested that in the presence of hematuria in patients with SCA, the possibility of renal cell cancer should be considered [9]. Since chronic organ damage and inflammation are in question in patients with SCA, malignant transformation can be observed as a result of cell damage [6]. CA15-3 and CA125 values may increase due to malignant transformation in patients with SCA. However, the patients included in our study had no known cancer focus. The low oxygen pressure and slow flow system in the arterial circulation facilitates the polymerization of sickle cells. This leads to chronic complications of the disease as a result of hypoxia and endothelial damage. We thought that the significant increase in CA15-3 measurements developed due to hypoxia and endothelial damage that developed during the course of the disease. Myocardial infarction is seen in patients with SCA rather than atherosclerotic coronary artery disease, due to increased oxygen demand and insufficient oxygen carrying capacity [10] . This result suggests that SCA directly causes endothelial damage by hypoxia. Zeferos et al. found that CA15-3 levels were significantly higher in hemodialysis patients [11]. Tzitzikos et al. found CA15-3 elevation in hemodialysis patients with hepatitis C infection and associated this situation with hepatitis C infection from the concomitant [12]. In our study, patients with high CA15-3 levels may have hepatitis C infection due to transfusion. This situation can be evaluated with a further study.

Erbağcı et al. found increased CA 15-3 levels in healthy women in the midluteal phase of the menstrual cycle compared to the midfollicular phase [13]. Novelli et al. stated that sickling in erythrocytes causes damage to the membrane structure and that abnormally expressed adhesion molecules with this damage are responsible for the premature elimination of erythrocytes in the reticuloendothelial system [14]. Leukocytosis develops as a result of the ischemia-reperfusion cycle and oxidative stress that develops during acute events, and the increase in endothelial cell adhesion molecules and inflammatory cytokines [13]. With these two mechanisms, they revealed a pathophysiology supporting the high levels of a membrane protein MUC 1 and its epitope, CA 15-3, in patients with SCA in our study.

In our study, although CA125 values were found at similar rates in the control and patient groups, there are many cases in which CA125 is elevated outside of malignancies. Kouris et al. showed that there is a direct correlation between CA 125's severity of congestive heart failure and fluid congestion [15].

Kaya et al. showed in their study that CA 125 has a predictive value for atrial fibrillation in patients with HF. [16]. Kouris et al. found that CA125 was an independent predictive value for rehospitalization in patients with congestive heart failure [17]. In our study, the ejection fraction was normal in the control and SCA group in echocardiographic examinations, and no signs of pericardial effusion were found.

Yücel et al. showed in their study that high CA125 values have a predictive value for the development of atrial fibrillation in patients with systolic heart failure [18]. Zhuang et al. showed that CA125 increased in HF patients in correlation with echocardiographic parameters, BNP and N-terminal pro-BNP [19]. In a study by Sílvia et al., they found a significant relationship between low systolic and diastolic blood pressure, low BMI and high CA125 values in patients with heart failure. It has also been suggested that CA125 is associated with poor prognosis and increased mortality [20].

In the study of Yılmaz et al., CA 125 values were shown to be significant in the evaluation of tuberculosis activity [21]. Mansour et al. stated that the CA125 and CEA levels of a patient with tuberculosis were high in the active period of the disease, and these values decreased in the post-treatment period [22]. Topalak et al found that regardless of the source of the disease, there was uptake in serosal fluids with high CA125 values [23]. In the study of Miralles et al., it was found that cardiovascular and chronic liver diseases were the most common in patients with high CA125 values, except for malignant diseases [24]. Sevinç et al found high CA125 values in patients with nephrotic syndrome without malignancy. It has also been reported that these patients have ascites detected by Ultrasonography [25]. In our study, no cancer focus was found in patients with elevated tumor markers, and the patients were followed up for the development of new cancer. We predict that CA15-3 and CA125 values may be found to be even higher in blood samples taken during acute events, which is one of the exclusion criteria of our study. Since it is a situation that we expect the parameters that can increase even in the case of chronic hypoxia to increase in the case of acute hypoxia, and we can consider this situation as a missing part of our study.

Limitations

There are some limitations in our study. Our study is limited because it was single-centered and studied with a small number of patients. However, our results are valuable in terms of pioneering other studies.

Conclusion

In our study, although the CA15-3 level was high in patients with SCA, the CA125 level was normal. We think that CA15-3 level is especially important in understanding the pathophysiology and mechanism of SCA and in terms of follow-up. In addition, our study is important in terms of investigating the relationship between other tumor markers and SCA. Our study should be supported by studies with large patient participation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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